

# Identity, Similarity, and Difference between Large Cell Neuroendocrine Carcinoma and Small Cell Carcinoma

## To the Editor:

I read the article entitled “Should large cell neuroendocrine lung carcinoma be classified and treated as a small cell lung cancer or with other large cell carcinomas?” by Varlotto et al.<sup>1</sup> with great interest. Knowing that the World Health Organization classification for the lung tumors is being revised, how to deal with the tumors with neuroendocrine features/morphology is one of the greatest issues in the revision process, and it remains as a great concern to not only pathologists but also many clinicians.

In this retrospective study, the authors retrieved 1211 patients with large cell neuroendocrine carcinoma (LCNEC), 8295 patients with other large cell carcinomas (OLC), and 35,304 patients with small cell lung carcinoma (SCLC) from the Surveillance Epidemiology and End Results (SEER) database from 2001 through 2007. They focused on the demographic and prognostic (overall survival and lung cancer-specific survival) differences among these three histologic types. The authors concluded that the clinical, histopathologic, and biologic features of LCNEC were more similar to OLC than to SCLC.

On the other hand, we have compared the demographics and prognosis of 141 LCNECs, 113 SCLCs, and other lung tumors with/without neuroendocrine features including 33 large cell carcinomas.<sup>2</sup> These cases were all resected surgically with enough specimens for central pathologic review by

expert panel. The results indicated that LCNEC and SCLC share the common demographic background and prognoses, and therefore, we have concluded that these two histologies belong to the same high-grade neuroendocrine tumors of the lung. This was an opposite conclusion to the study by Varlotto et al.

In discussing the similarities/differences among different histopathologic types, the establishment of the correct, reliable diagnosis is a key issue. Especially for the diagnosis of tumors with neuroendocrine morphology/phenotype, the diagnosis needs to demonstrate not only the histopathologic neuroendocrine morphology but also the neuroendocrine phenotype by electron microscope or immunohistochemistry. As for LCNEC, the morphology is to be characterized by the organoid nesting, trabecular growth, rosette formation, palisading, necrosis, and high mitotic figures.<sup>3</sup> The World Health Organization classification further strictly requires the immunohistochemistry using neuroendocrine markers such as chromogranin, synaptophysin, and neural cell adhesion molecule. The demonstration of specific neuroamines, neuropeptide, or hormone is also permitted. In our previous study, such process was all centralized with the review by expert pathologists to confirm the neuroendocrine morphology/phenotype.

Herein, I raise the question regarding the histologic diagnosis in the study by Varlotto et al. The authors used the registry data of SEER simply with the code of histologic diagnosis as “LCNEC,” “OLC,” or “SCLC.” However, how strictly were these diagnosis made? How sure were they? As was written by the authors, “distinguishing LCNEC from SCLC can occasionally be difficult,” even with the aid of the immunohistochemical study, and the quality of diagnosis wholly depends on how strictly each histologic criterion was examined. In the SEER database, it might have happened that number of cases currently classified as LCNEC could have been previously included in the SCLC or OLC category and vice versa. According to the authors, “such misclassification could potentially mask differences in presenting characteristics and outcome between LCNEC and SCLC.”

This is really a crucial point especially in discussing the biological identity, similarity, and difference among different morphologies. The issue in the article by Varlotto et al. is the reliability of the histologic diagnosis because of the nature of the data, a registry database.

In our previous study, both LCNEC and SCLC could be characterized as the high-grade neuroendocrine carcinoma. They were more likely to arise among elderly men (LCNEC, 89.4%; SCLC, 79.9%) with heavy smoking history (LCNEC, 98.6%; SCLC, 93.8%). These similar backgrounds and prognoses of two different histologies have suggested that these tumors are closely located in the malignant spectrum of the lung tumors despite the morphologic difference.<sup>4</sup> In the study by Varlotto et al., however, men comprised only 55.2% of LCNEC and 48.5% of SCLC, and the smoking history was not clearly shown. Looking at these data, I am not sure whether tumors in our previous study were really same as those in the study by Varlotto et al.

How to deal both LCNEC and SCLC with neuroendocrine features in the classification of the lung tumors is relevant to how to manage the patients with these histologies. The present therapeutic schema is wholly based on the histology as SCLC or non-small cell carcinoma, and therefore, the clinicians are very much concerned about the future revision of the histologic classification of lung tumors.

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Disclosure: The author declares no conflicts of interest.

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